

# THE RELATIONSHIP BETWEEN GRAM-NEGATIVE COLONISATION AND BLOODSTREAM INFECTIONS IN NEONATES: A SYSTEMATIC REVIEW AND META-ANALYSIS

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## Search strategy

**MEDLINE (Ovid MEDLINE(R) without Revisions 1996 to June Week 2 2016) and EMBASE (Embase 1996 to 2016 Week 24)**

#1 neonate.mp. or exp Infant, Newborn/

#2 infant.mp. or exp Infant/

#3 newborn.mp.

#4 1 or 2 or 3

#5 Bacteria/ or routine culture.mp.

#6 surface culture.mp.

#7 microbiological screening.mp.

#8 colonisation.mp.

#9 Infant, Premature, Diseases/ or exp Carrier State/ or surveillance culture.mp.

#10 carrier state.mp. or exp Carrier State/

#11 swab.mp.

#12 Carrier State/ or carriage.mp.

#13 colonization.mp.

#14 superficial culture.mp.

#15 rectal swab.mp.

#16 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15

#17 exp Sepsis/ or sepsis.mp.

#18 bacteremia.mp. or exp Bacteremia/

#19 exp Sepsis/ or septicaemia.mp. or exp Bacteremia/

#20 exp Cross Infection/ or exp Bacteremia/ or exp Bacterial Infections/ or bloodstream infection.mp. or exp Sepsis/

#21 systemic inflammatory response syndrome.mp. or exp Systemic Inflammatory Response Syndrome/

#22 septi\*.mp.

#23 septicaemi\*.mp.

#24 17 or 18 or 19 or 20 or 21 or 22 or 23

#25 4 and 16 and 24

#26 limit 25 to yr="2000 -Current"

#27 limit 26 to humans

### **COCHRANE LIBRARY (Issue 6 of 12, June 2016)**

#1 MeSH descriptor: [Infant, Newborn] explode all trees

#2 "newborn":ti,ab,kw (Word variations have been searched)

#3 "neonate":ti,ab,kw (Word variations have been searched)

#4 MeSH descriptor: [Infant] explode all trees

#5 "infant":ti,ab,kw (Word variations have been searched)

#6 1 or 2 or 3 or 4 or 5

#7 routine culture:ti,ab,kw (Word variations have been searched)

#8 surface culture:ti,ab,kw (Word variations have been searched)

#9 microbiological screening:ti,ab,kw (Word variations have been searched)

#10 "colonization":ti,ab,kw (Word variations have been searched)

#11 "colonisation":ti,ab,kw (Word variations have been searched)

#12 MeSH descriptor: [Carrier State] explode all trees

#13 "carrier state":ti,ab,kw (Word variations have been searched)

#14 "surveillance culture":ti,ab,kw (Word variations have been searched)

#15 "swab":ti,ab,kw (Word variations have been searched)

#16 "rectal swab":ti,ab,kw (Word variations have been searched)

#17 "carriage":ti,ab,kw (Word variations have been searched)

#18 superficial culture:ti,ab,kw (Word variations have been searched)

#19 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18

#20 MeSH descriptor: [Sepsis] explode all trees

#21 "sepsis":ti,ab,kw (Word variations have been searched)

#22 MeSH descriptor: [Bacteremia] explode all trees

#23 "bacteremia":ti,ab,kw (Word variations have been searched)

#24 "bacteraemia":ti,ab,kw (Word variations have been searched)

#25 "septicaemia":ti,ab,kw (Word variations have been searched)

#26 "septicemia":ti,ab,kw (Word variations have been searched)

#27 "bloodstream infection":ti,ab,kw (Word variations have been searched)

#28 MeSH descriptor: [Systemic Inflammatory Response Syndrome] explode all trees

#29 "systemic inflammatory response syndrome":ti,ab,kw (Word variations have been searched)

#30 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29

#31 6 and 19 and 30

**Table 1S: Characteristics of the included studies**

Author, year	Country	GDP	Study period	Study design	During outbreak? (Yes/No)	Inclusion criteria	Exclusion criteria	Outcome definition	Quality of reporting#	Quality assessment##
<b>BABY LEVEL</b>										
<b>Akturk H, 2016 [1]</b>	Turkey	UMIC	Jan 2010- Dec 2014	retrospective surveillance study	N	all pts admitted to NICU	nr	(1) Carbapenem-resistant (CR) <i>Klebsiella pneumoniae</i> (KP) BSI in previously colonised pts (cases) (2) CRKP colonised patients who did not developed CRKP infection (controls)	45.7	selection: **  comparability: 0  outcome: **
<b>Almuneef MA, 2001 [2]</b>	US	HIC	Jan-Mar 1997	prospective surveillance study	N	all pts admitted to NICU	nr	not defined	32.6	selection: **  comparability: 0  outcome: **
<b>Biran V, 2010 [3]</b>	France	HIC	Jan 2000- Dec 2009	prospective surveillance study	N	all pts admitted to NICU	(1) pre-colonised with ESBL  (2) vertical infections	(1) isolation of ESBL from rectal swab (colonisation)  (2) isolation of ESBL from BC (infection)  in neonates >72h of age and >48h of hospital admission	8.7	selection: **  comparability: 0  outcome: **

<b>Boo NY, 2005 [4]</b>	Malaysia	UMIC	Jan-Jun 2000	retrospective study	N	all pts admitted to NICU	>28 days of life	(1) neonates colonised by ESBL- <i>Klebsiella spp.</i> (cases) (2) neonates non-colonised by ESBL- <i>Klebsiella spp.</i> during the 14-days preceding the date of the case (controls) (3) BC positive for ESBL- <i>Klebsiella spp.</i> with clinical features (sepsis)	57.6	selection: ** comparability: * outcome: **
<b>Graham PL, 2007 [5]</b>	US	HIC	Jan 2004-Sep 2005	prospective surveillance study	N	VLBW pts ≤7 d of life	nr	genotypically concordant colonising flora and BC	35.1	selection: ** comparability: 0 outcome: **
<b>Gundes S, 2005 [6]</b>	Turkey	UMIC	7 weeks period (not specified)	prospective cohort study	Y	all pts admitted to NICU	nr	defining the role of follow-up rectal swabs during an outbreak	31.9	selection: ** comparability: ** outcome: *
<b>Mammaia C, 2008 [7]</b>	Italy	HIC	Jan 2003-Jan 2004	prospective surveillance study	N	all pts admitted for at least 48 h	nr	(1) rectal swab positive for GNB without clinical symptoms (colonisation); (2) nosocomial infection identified according to the CDC	51.1	selection: ** comparability: ** outcome: **

<b>Mustapa M, 2014 [8]</b>	UK	HIC	Jan 2010- Dec 2013	retrospective cohort study	N	all inborn ELBW infants	nr	concordant positive BC	na	selection: ***  comparability: *  outcome: **
<b>Oteo J, 2013 [9]</b>	Spain	HIC	Sep 2010- Dec 2011	nr	Y	all pts admitted to NICU	nr	infection or colonisation by ESBL-producing <i>Enterobacter cloacae</i>	27.1	selection: **  comparability: 0  outcome: **
<b>Parm U, 2011 [10]</b>	Estonia	HIC	Aug 2006- Nov 2007	prospective, cluster- randomized, two-centre study	N	(1) younger than 72 h; (2) needed AB on clinical suspicion and/or due to risk factors of infection; (3) expected to stay for >24 h	nr	(1) BC positive for GNB with clinical and lab signs of sepsis at ≥72 hr of life (late-onset sepsis) (2) rectal swab positive for GNB between 2 and 14 days before positive BC (colonisation)	41.5	selection: ***  comparability: **  outcome: **

<b>Pessoa-Silva CL, 2003 [11]</b>	Brazil	UMIC	Aug 1997- May 1999	prospective follow-up study	N	(1) pts admitted to NICU; (2) stayed at least 24 h; (3) had at least 1 sample on admission and 1 per week of hospitalization	nr	(1) any patient with symptoms or signs of infection and BC positive for ESBL- <i>K. pneumoniae</i> (sepsis); (2) rectal swab positive for ESBL- <i>K. pneumoniae</i> without symptoms or signs of infection (colonisation)	47.9	selection: ** comparability: ** outcome: **
<b>Singh N, 2002 [12]</b>	US	HIC	1998-2000	prospective surveillance study	N	all pts admitted to NICU	(1) admitted with preexisting rectal colonization; (2) no surveillance cultures taken; (3) multiple NICU admissions	(1) BC positive for antimicrobial non-susceptible <i>Enterobacteriaceae</i> (ANE) (sepsis); (2) rectal swab positive for ANE without signs of infection (colonisation)	48.9	selection: ** comparability: ** outcome: **
<b>Smith A, 2010 [13]</b>	US	HIC	Sep 2004- Oct 2007	prospective cohort study	N	VLBW infants	(1) parental refusal;	(1) BC positive for GNB in a VLBW infant $\geq 72$ hr after birth (sepsis);	42.6	selection: **

							(2) congenital anomalies making impossible to obtain samples;	(2) rectal swab positive for GNB with the same AST profile (colonisation)			comparability: **
							(3) age >14 days upon admission;				outcome: **
							(4) death within 48 hr of admission				
<b>Suviste J, 2012 [14]</b>	UK	HIC	Sep 2010- Mar 2012	prospective surveillance study	N	nr	nr	nr		na	selection: **  comparability: 0  outcome: **
<b>Velasco C, 2009 [15]</b>	Spain	HIC	Aug 2005- Feb 2006	prospective surveillance study	Y	all pts admitted to NICU	nr	nr		22.9	selection: **  comparability: 0  outcome: **



**UNIT LEVEL**

<b>Cassettari VC, 2009 [16]</b>	Brazil	UMIC	Nov 2004- Feb 2005	cross-sectional survey	Y	all pts admitted to NICU	nr	infection or colonisation by ESBL- <i>K. pneumoniae</i>	42.7	selection: ** comparability: ** outcome: **
<b>Das P, 2011 [17]</b>	India	LMIC	2007	prospective study	N	neonates who stayed in the hospital for at least 72 h	nr	clinical sepsis and culture-positive sepsis	58.5	selection: ** comparability: ** outcome: **
<b>Gbaguidi-Haore H, 2008 [18]</b>	France	HIC	Dec 2002- Dec 2004	prospective surveillance study	Y	all pts admitted to NICU	nr	(1) <i>E. cloacae</i> isolated from a rectal screening sample (colonisation) (2) positive BC (infection)	46.9	selection: ** comparability: 0 outcome: **
<b>Gupta A, 2004 [19]</b>	US	HIC	Sep 2000- Sep 2001	prospective surveillance study	Y	all pts admitted to NICU	nr	infants who have positive cultures	47.9	selection: ** comparability: ** outcome: **

<b>Haase R,</b>	Germany	HIC	Jan 2011-	prospective	N	all pts admitted	nr	(1) positive swab without symptoms of infections	43.6	selection: **
<b>2014 [20]</b>			Dec 2012	surveillance study		to NICU		(colonisation)  (2) neoKISS definition (sepsis)		comparability: **  outcome: **
<b>Litzow JM,</b>	Philippin	LMIC	May 2003-	prospective	N	all pts admitted	nr	colonisation with gentamicin or third generation	52.1	selection: **
<b>2009 [21]</b>	es		Aug 2004	study		to NICU		cephalosporin-resistant GNB		comparability: **  outcome: **
<b>Macnow</b>	US	HIC	Jan 2004 -	retrospective	N	(1) transferred	(1) admitted or	colonised if surveillance cultures positive for multidrug-	60.4	selection: **
<b>T, 2013</b>			Dec 2010	study		to the study	readmitted from	resistant (MDR) GNB		comparability: 0
<b>[22]</b>						NICUs from another facility and had 1 or more surveillance cultures obtained	home  (2) surveillance cultures not obtained  (3) surveillance cultures obtained  2 or more days after admission			outcome: **

						NICUs and then readmitted				
<b>Mamma C, 2007 [23]</b>	Italy	HIC	Jan 2003 - Jan 2004	prospective study	N	neonates who stayed in the hospital for at least 48 h	nr	colonisation with MDR-GNB	66.0	selection: **  comparability: 0  outcome: **
<b>Parm U, 2011 [24]</b>	Estonia	HIC	Aug 2006 - Nov 2007	prospective, cluster- randomized study	N	(1) younger than 72 h  (2) needed early empiric antibiotic treatment on clinical suspicion and/or due to risk factors of infection	nr	(1) preexisting mucosal colonisation defined as the presence of Gram-negative micro-organisms on mucosal surfaces two to 14 days before the collection of sterile fluid cultures  (2) late-onset sepsis diagnosed if GNB cultured from normally sterile body fluids, and clinical and laboratory signs of sepsis were present at 72 h of life	67.0	selection: ***  comparability: 0  outcome: **

						(3) expected to stay in unit for >24 h				
<b>Rettedal S, 2013 [25]</b>	Norway	HIC	Nov 2008 – Apr 2010	retrospective study	Y	all pts admitted to NICU	nr	(1) ESBL-producing <i>K. pneumoniae</i> colonisation: isolation of ESBL-producing <i>K. pneumoniae</i> from faecal or rectal samples in patients without clinical symptoms or signs of infection  (2) ESBL-producing <i>K. pneumoniae</i> infection: any NICU patient with symptoms or signs of systemic infection and ESBL-producing <i>K. pneumoniae</i> isolation from blood, urine or cerebrospinal fluid	43.8	selection: **  comparability: 0  outcome: **
<b>Richards C, 2004 [26]</b>	Colombia	UMIC	nr	point prevalence survey	Y	all pts admitted to high-risk NICU	nr	<i>K. pneumoniae</i> colonisation and BSI	46.9	selection: **  comparability: 0  outcome: *
<b>Roy S, 2010 [27]</b>	India	LMIC	2007	nr	N	all pts admitted to NICU	nr	gut colonization with MDR <i>Acinetobacter baumannii</i> among hospitalised neonates	50.0	selection: ***  comparability: *

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Abbreviations: <sup>a</sup>GDP: Gross domestic product; <sup>b</sup>UMIC: Upper Middle Income Countries; <sup>c</sup>NICU: Neonatal Intensive Care Unit; <sup>d</sup>BSI: Bloodstream Infection; <sup>e</sup>HIC: High Income Countries; <sup>f</sup>ESBL: Extended-spectrum beta-lactamase; <sup>g</sup>BC: blood culture; <sup>h</sup>VLBW: Very Low Birth Weight; <sup>i</sup>GNB: Gram-negative bacteria; <sup>j</sup>ELBW: Extremely Low Birth Weight; <sup>m</sup>LMIC: Lower Middle Income Countries. nr: Not Reported; na: Not Applicable; <sup>#</sup>Percentage of STROBE-NI items adequately reported; <sup>##</sup>Assessed by the Newcastle-Ottawa Scale for non-randomized studies in meta-analysis

**Table 2S: Microbiological assessment**

Author, year	Type of screening	Timing (frequency) of screening	Detected bacteria	AST performed	Genotyping
<b>BABY LEVEL</b>					
<b>Akturk H, 2016 [1]</b>	Rectal swabs	once a week	Carbapenem-resistant <i>Klebsiella pneumoniae</i>	disk diffusion (CLSI); E-test (carbapenem-resistance)	nr
<b>Almuneef MA, 2001 [2]</b>	Rectal swabs	on admission, weekly, and on discharge	Gram-negatives	disc diffusion	pulsed field gel electrophoresis (PFGE )
<b>Biran V, 2010 [3]</b>	Rectal swab	on admission and every  10 days	ESBL- <i>Enterobacteriaceae</i>	nr	nr
<b>Boo NY, 2005 [4]</b>	Rectal swabs	on admission, at  weekly interval	ESBL- <i>Klebsiella spp</i>	double disk  diffusion	nr
<b>Graham PL, 2007 [5]</b>	Rectal swabs	weekly until discharge	Gram-negatives	Microscan Walk Away  SI System	PFGE

<b>Gundes S, 2005 [6]</b>	Rectal swabs	twice a week	ESBL- <i>K. pneumoniae</i>	double disk diffusion	Polymerase chain reaction (PCR)
<b>Mamina C, 2008 [7]</b>	Rectal swabs	twice a week throughout the NICU stay	MBL-producing <i>Pseudomonas aeruginosa</i>	disk diffusion	PCR
<b>Mustapa M, 2014 [8]</b>	Skin swab	on admission	<i>Escherichia coli</i>	nr	nr
<b>Oteo J, 2013 [9]</b>	Rectal swabs	once a week until discharge	ESBL-producing <i>Enterobacter cloacae</i>	automated MicroScan microdilution system	PCR
<b>Parm U, 2011 [10]</b>	Rectal swabs	on admission and twice a week	Gram-negatives	nr	nr
<b>Pessoa-Silva CL, 2003 [11]</b>	Rectal swabs	within 48 h of admission and weekly until discharge	ESBL-producing <i>K. pneumoniae</i>	GNS-650 card with ESBL test and by disk-diffusion	PFGE
<b>Singh N, 2002 [12]</b>	Rectal swabs	on admission and weekly	antimicrobial-non susceptible <i>Enterobacteriaceae</i> (ANE)	disk diffusion	nr

<b>Smith A, 2010 [13]</b>	Rectal swabs	weekly until discharge	Gram-negatives	MicroScan WalkAway SI System	nr
<b>Suviste J, 2012 [14]</b>	Rectal swab	on admission and weekly	<i>Serratia</i> , gentamicin-resistant or ESBL-producing <i>Enterobacteriaceae</i> , <i>P. aeruginosa</i>	nr	nr
<b>Velasco C, 2009 [15]</b>	Rectal swab	on admission and weekly	ESBL-producing <i>K. pneumoniae</i>	broth microdilution	PFGE
<b>UNIT LEVEL</b>					
<b>Cassettari VC, 2009 [16]</b>	Rectal swab	on a weekly basis	ESBL-producing <i>K. pneumoniae</i>	double-disk synergy test	PFGE
<b>Das P, 2011 [17]</b>	Rectal swab	within 4 h of birth and then within the next 3–7 days	Gram-negative Bacilli	disk diffusion	PFGE
<b>Gbaguidi-Haore H, 2008 [18]</b>	Rectal swab	on admission and once a week thereafter	<i>E. cloacae</i>	disk diffusion	PFGE
<b>Gupta A, 2004 [19]</b>	Rectal swab	twice a week	ESBL <i>K. Pneumoniae</i>	E-test	PFGE
<b>Haase R, 2014 [20]</b>	Rectal swab	on admission and weekly	MDR Gram-negatives	nr	PFGE



<b>Litzow JM, 2009</b> [21]	Stool or peri-rectal swab	NICU day 0,2,7; weekly and on the day of discharge	Gram-negatives	disk diffusion	nr
<b>Macnow T, 2013</b> [22]	Rectal swab	on admission	Gram-negatives	disk diffusion	nr
<b>Mamina C, 2007</b> [23]	Rectal swab	twice a week	MDR Gram-negatives	disk diffusion	PFGE
<b>Parm U, 2011</b> [24]	Rectal swab	on admission and twice a week	common aerobic Gram-negatives	nr	nr
<b>Rettedal S, 2013</b> [25]	Rectal swab (faecal or rectal samples)	nr	ESBL-producing <i>Enterobacteriaceae</i>	disk diffusion	PFGE
<b>Richards C, 2004</b> [26]	Rectal swab	nr	<i>K. Pneumoniae</i>	MicroScan WalkAway	nr
<b>Roy S, 2010</b> [27]	Stool culture	nr	MDR <i>Acinetobacter baumannii</i>	double disk diffusion	PCR, PFGE, and BigDye Terminator v3.1 Cycle Sequencing Kit

Abbreviations: <sup>a</sup>AST: Antimicrobial Susceptibility Testing; <sup>b</sup>CLSI: Clinical & Laboratory Standards Institute; <sup>c</sup>ESBL: Extended-spectrum beta-lactamase; <sup>d</sup>NICU: Neonatal

Intensive Care Unit; <sup>e</sup>MBL: metallo beta lactamase; <sup>f</sup>MDR: Multidrug-resistant. nr: Not Reported

**Table 3S: Rate of colonisation and prevalence of Bloodstream Infections in studies included in the baby-level analysis**

Author, year	Gestational age in weeks (%)	Birth weight in grams (%)	Age in days at screening	Sex (%)	Length of follow-up	Interval between positive screening and onset of BSI	Population (n of screened babies)	n of colonised babies	n of non-colonised babies	n of colonised infected babies (same organism)	n of non-colonised infected babies	Prevalence of concordant GN-BSI in colonised babies (%)
<b>Akturk H, 2016 [1]</b>	nr	nr	nr	nr	nr	10.6 ± 1.9 days (median: 7 days, range: 2–38 days)	1,671	44	1,627	8	nr	18.2
<b>Almuneef MA, 2001 [2]</b>	24-29 (23) 30-36 (43) >36 (34)	450–1500 (16) 1501–2500 (24) >2500 (60)	median 2	M 51	nr	nr	239	89	150	10	0	11.2
<b>Biran V, 2010 [3]</b>	nr	nr	nr	nr	nr	nr	nr	46	nr	3	nr	6.5
<b>Boo NY, 2005 [4]</b>	mean 33.9 ±4.5 SD	mean 1975	median 9 (IQR 13)	M 61.3	nr	nr	368	80	288	5	4	6.2
<b>Graham PL, 2007 [5]</b>	nr	<1500	nr	nr	nr	range 1-17 days	nr	221	nr	19	nr	8.6

<b>Gundes S,</b>	nr	nr	nr	nr	nr	nr	49	8	41	2	5	25.0
<b>2005 [6]</b>												
<b>Mamina C, 2008 [7]</b>	24–29 (6.2)	≤ 500 (0.9)	median 13	M	22.3 d	nr	210	36	174	0	nr	0.0
	30–36 (47.1)	501–1000 (5.2)		50.5	median							
	> 36 (46.7)	1001–1500 (8.1)			13 d,							
		1501–2000 (21.4)			range 3– 140							
		2001–2500 (17.1)										
		> 2500 (47.3)										
<b>Mustapa M,</b>	nr	<1000	nr	nr	nr	nr	161	11	150	4	nr	36.4
<b>2014 [8]</b>												
<b>Oteo J, 2013 [9]</b>	nr	nr	nr	M	until 50	nr	413	7	406	3	4	42.8
					discharge							
<b>Parm U,</b>	<28 (33.3)	≤1000 (27.2)	nr	M	nr	median 10.5 days	278	154	124	16	51	10.4
<b>2011 [10]</b>	≥37 (19.9)	≤1500 (51.5)		57		(range 2-36) for Enterobacteriaceae and 7 days (range						
		≥2500 (24.3)										

2-29) for non-fermentative micro-organisms												
<b>Pessoa-Silva CL, 2003 [11]</b>	nr	<1500 (16)	nr	M	until discharge	median 5 days (range: 3- 23 days)	380	219	161	9	4	4.1
<b>Singh N, 2002 [12]</b>	nr	<1000 (28)	42 ±3 SEM	M	mean 48 ± 3 days	nr	1,410	240	1,170	9	nr	3.7
		1001–1500 (10)		54								
		1501–2500 (22)										
		>2500 (40)										
<b>Smith A, 2010 [13]</b>	mean 28.2 ±2.6 SD	≤750 (22.6)	nr	M	mean 48.1	mean of 6 days (median 6; range, 1–17 days)	698	625	73	59	0	9.4
		751-1000 (26.1)		48.1	50.7 days							
		1001-1250 (25.6)			(SD 38.2)							
		1251-1500 (25.5)										
<b>Suviste J, 2012 [14]</b>	nr	nr	nr	nr	nr	nr	2,101	45	2,056	1	9	2.2

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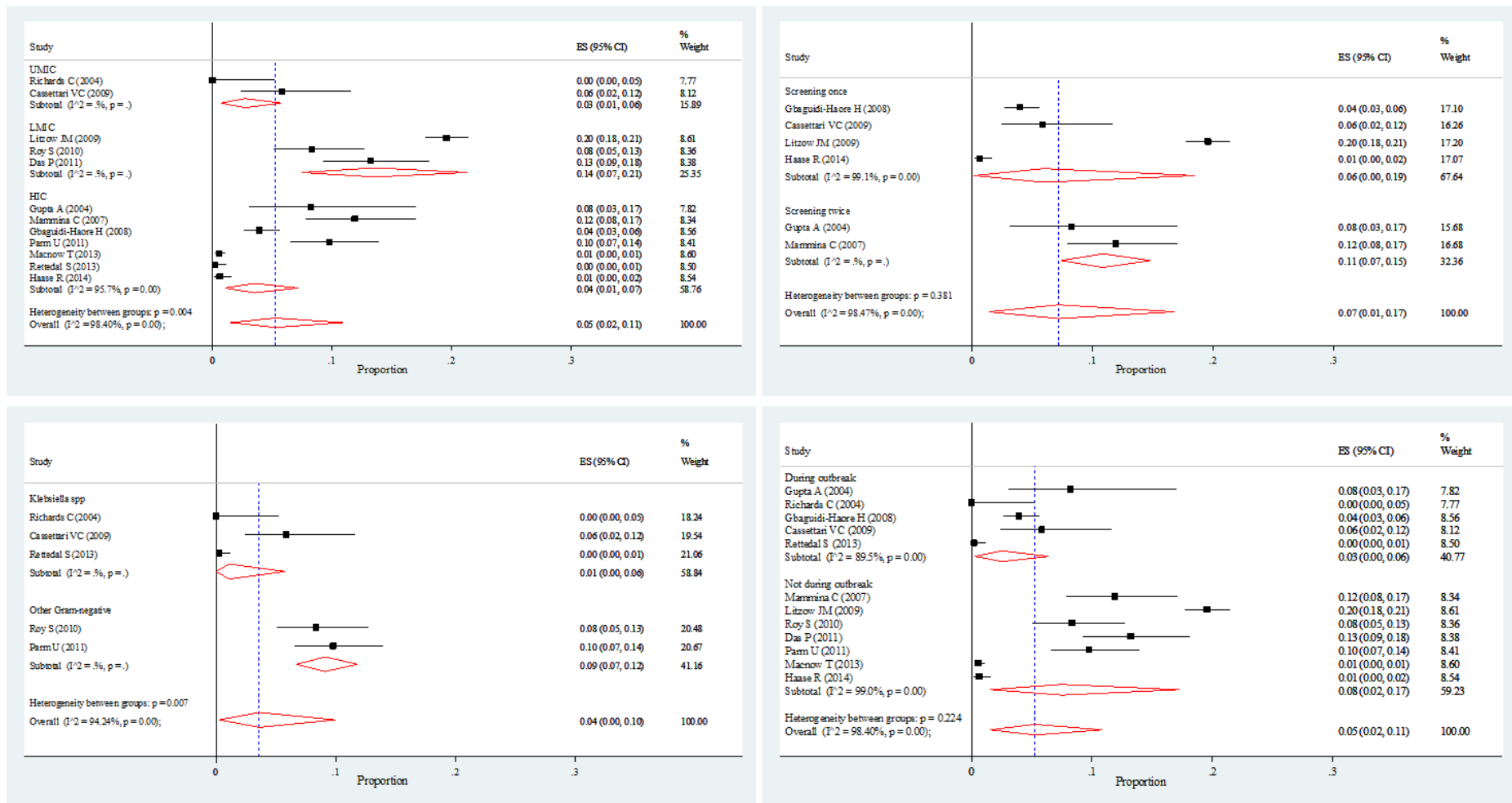
Velasco C,	nr	nr	nr	nr	until	nr	443	159	284	9	8	5.7
2009 [15]					discharge							

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Abbreviations: <sup>a</sup>GN-BSI: Gram-negative Bloodstream Infection; <sup>b</sup>M: males; <sup>c</sup>SD: standard deviation; <sup>d</sup>IQR: Interquartile Range; <sup>e</sup>SEM: Standard Error of Mean. nr: Not

Reported

Figure 1S: Meta-regression analysis by different groups at the unit-level



\*Weighting are assigned with a random-effect model using the Freeman-Tukey double arsine transformation. Abbreviations: CI, confident interval; ES, effect size. HIC, high income country; LMIC, lower middle income country; UMIC, upper middle income country.

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